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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/559,383	12/06/2005	Klaus Dietzel	27072U	3631

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NATH & ASSOCIATES PLLC
112 South West Street
Alexandria, VA 22314

EXAMINER	
ALSTRUM ACEVEDO, JAMES HENRY	
ART UNIT	PAPER NUMBER
1616	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/559,383	DIETZEL ET AL.	
	Examiner	Art Unit	
	JAMES H. ALSTRUM ACEVEDO	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☒ Claim(s) *2,4,8 and 10* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/7/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-11 are pending. Applicants amended claims 1-11 in a preliminary amendment, submitted December 6, 2005.

Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Claim Objections

Claims 2, 4, 8, and 10 are objected to because of the following informalities: the phrase "further comprising" or "further," as appropriate, should be inserted (i) after the word "optionally" in claim 2, (ii) before "a surfactant" in claim 4, (iii) before the word "comprises" in claim 8, and (iv) and before the word "comprising" in claim 10, because, although the parent claim of said claims utilize open comprising language, and it is understood that the claimed composition of the parent independent claim may contain additional components, parent claim 1 does not make reference to surfactants, oleic acid, and disodium chromoglycate. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement (lack of written description for solvates and physiologically functional derivatives). The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Determination of Claim Scope

The rejected claims claim a pharmaceutical suspension formulation comprising (i) the active particles of ciclesonide, physiologically functional derivative, ***solvate***, or salt thereof, (ii) particles of formoterol, salt, , physiologically functional derivative, fumarate dihydrate thereof, or ***solvate thereof***, (iii) HFA 134a (i.e. 1,1,1,2-tetrafluoroethane), HFA 227 (i.e. 1,1,1,2,3,3,3-heptafluoropropane), or mixtures thereof, and (iv) optionally surfactant.

Review of Applicants' Disclosure

The instant specification does not disclose, to which solvates of ciclesonide and formoterol (i.e. excluding formoterol fumarate dihydrate) Applicants are referring. Applicants' specification does not disclose how to make any particular solvate or hydrate of ciclesonide or formoterol, nor do Applicants depict chemical structures of ciclesonide and formoterol as any particular hydrate or solvate in their disclosure. Hydrates are recognized as being a sub-genus of solvates in which the "solvent" molecule is water.

Possession Based on Ordinary Skilled Artisan's Determination/ State of the Prior Art

It is generally accepted in the art that the formation of a particular solvate, polymorph, or hydrate for a given compound or series of compounds is unpredictable (see Vippagunta et al. "Crystalline Solids," *Advanced Drug Delivery Reviews*, **2001**, *48*, 1-26, especially pp 1, 11-12, and 18), therefore, the generic reference to a solvate of either ciclesonide or formoterol in the instant specification does not provide adequate written support for claims drawn to any solvate or hydrate of these compounds, with the exception of formoterol fumarate dihydrate, which is known from Trofast et al. (U.S. Patent No. 5,434,304: col. 6, line 10 through col. 7, line 27), for example. Ciclesonide and its epimers are known from U.S. Patent No. 5,482,934 (IDS). Braga et al. (*Chem. Commun.*, "Making Crystals from Crystals: a green route to crystal engineering and polymorphism," **2005**, pp 3635-3645) states on page 3640,

> "One can say that if the formation of polymorphs is a nuisance for crystal engineers, ***solvate formation can be a nightmare***, because it is extremely difficult to predict whether a new species may crystallize[s] from solution with one or more molecules of solvent."

An ordinary skilled artisan would conclude that Applicants were not in possession of any particular solvate or hydrate of any of compounds (i) and (ii) described above, with the exception of formoterol fumarate dihydrate. Furthermore, because Applicants' generic reference to solvates of ciclesonide and formoterol does not permit the ordinary skilled artisan to clearly envisage what specific ciclesonide and formoterol solvates, with the exception of formoterol fumarate dihydrate, were in Applicants' possession, the only reasonable conclusion said artisan would make was that Applicants were not in possession of the genus of solvates, including the sub-genus of hydrates of ciclesonide and formoterol and had not reduced to practice the

preparation, isolation, and characterization of said solvates and hydrates, with the exception of formoterol fumarate dihydrate, which was known in the prior art.

The remaining claims are rejected as depending from a rejected claim.

Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a pharmaceutical suspension formulation comprising (i) the active particles of ciclesonide, an epimer or salt thereof, or 16-alpha-,17-(22R,S)-Cyclohexylmethylendioxy-11-beta-21-dihydroxypregna--1,4-dien-3,20-dione, 16-alpha-,17-(22R)-Cyclohexylmethylendioxy-11-beta-21-dihydroxypregna-1,4-dien-3,20-dione (ii) particles of formoterol, salts, stereoisomers, or the fumarate dihydrate thereof, (iii) HFA 134a (i.e. 1,1,1,2-tetrafluoroethane), HFA 227 (i.e. 1,1,1,2,3,3,3-heptafluoropropane), or mixtures thereof, and (iv) optionally surfactant, does not reasonably provide enablement for said pharmaceutical suspension composition comprising the solvate, any physiologically functional derivative of particulate ciclesonide and/or of particulate formoterol. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

An analysis based upon the Wands factors is set forth below.

To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. In *Genentech Inc. v. Novo Nordisk* 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997); *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993),. See also *Amgen*

Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir. 1991); *In re Fisher* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Further, in *In re Wands* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) the court stated:

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman (230 USPQ 546, 547 (Bd Pat App Int 1986)). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Breadth of Claims

Applicants' claims are broad with regards to the genera of solvates, hydrates, physiologically acceptable salts, and physiologically functional derivatives of ciclesonide and formoterol. Applicants have defined the term "physiologically functional derivative" with regards to ciclesonide in paragraph [0017], "a chemical derivative of ciclesonide having the same physiological function as ciclesonide, for example, by being convertible in the body thereto or by being an active metabolite of ciclesonide." The term physiologically acceptable derivative with regards to formoterol is defined in paragraph [0018], "a chemical derivative of formoterol having the same physiological function as the free compound, for example, by being convertible in the body thereto."

Nature of the invention/State of the Prior Art

Claims 1-11 of the instant application claim a pharmaceutical suspension formulation comprising (i) the active particles of ciclesonide, ***physiologically functional derivative***, ***solvate***, or salt thereof, (ii) particles of formoterol, salt, ***physiologically functional derivative***, fumarate

dihydrate thereof, or ***solvate thereof***, (iii) HFA 134a (i.e. 1,1,1,2-tetrafluoroethane), HFA 227 (i.e. 1,1,1,2,3,3,3-heptafluoropropane), or mixtures thereof, and (iv) optionally surfactant and thereof are representative of the nature of Applicants' invention. It is generally accepted in the art that the formation of a particular solvate or hydrate for a given compound or series of compounds is unpredictable (see Vippagunta et al. "Crystalline Solids," *Advanced Drug Delivery Reviews*, **2001**, *48*, pp 11 and 18). Braga et al. (*Chem. Commun.*, "Making Crystals from Crystals: a green route to crystal engineering and polymorphism," **2005**, pp 3635-3645) states on page 3640, "One can say that if the formation of polymorphs is a nuisance for crystal engineers, solvate formation can be a nightmare, because it is extremely difficult to predict whether a new species may crystallize[s] from solution with one or more molecules of solvent." A search of the art fount that the art discloses the preparation of a single specific solvate of formoterol or a formoterol derivative: formoterol fumarate dihydrate (Trofast et al., U.S. Patent No. 5,434,304: col. 6, line 10 through col. 7, line 27). No specific solvates or hydrates of ciclesonide were uncovered. Ciclesonide and its epimers are known from U.S. Patent No. 5,482,934 (IDS).

Level of One of Ordinary Skill & Predictability/Unpredictability in the Art

The level of a person of ordinary skill in the art is high, with ordinary artisans having advanced medical and/or scientific degrees (e.g. M.D., Ph.D., Pharm. D. or combinations thereof). There is a general lack of predictability in the pharmaceutical art. *In re Fisher*, 427, F. 2d 833, 166, USPQ 18 (CCPA 1970). The art is especially unpredictable with regards to the existence and formation of particular polymorphs and pseudopolymorphs (e.g. hydrates and

solvates) of chemical compounds, as set forth above by the teachings of Vippagunta et al. and Braga.

Guidance/Working Examples

Applicants provide no guidance or working examples about the preparation of any solvate or hydrate of ciclesonide and formoterol. The only physiologically active derivatives of ciclesonide disclosed by Applicants are identified in paragraph [0017] of the specification. Paragraph [0017] provides no guidance as to what modifications are necessary to obtain a compound that is a physiologically functional derivative of ciclesonide per Applicants' definition in paragraph [0017]. Similarly, paragraph [0018] of Applicants' specification does not identify any particular chemical modifications that afford physiologically functional formoterol derivatives, Aside from identifying stereoisomers of formoterol as being physiologically active (e.g. R,R-formoterol).

In conclusion, the specification, while being enabling for a pharmaceutical suspension formulation comprising (i) the active particles of ciclesonide, an epimer or salt thereof, or 16-alpha-,17-(22R,S)-Cyclohexylmethylendioxy-11-beta-21-dihydroxypregna--1,4-dien-3,20-dione, 16-alpha-,17-(22R)-Cyclohexylmethylendioxy-11-beta-21-dihydroxypregna-1,4-dien-3,20-dione (ii) particles of formoterol, salts, stereoisomers, or the fumarate dihydrate thereof, (iii) HFA 134a (i.e. 1,1,1,2-tetrafluoroethane), HFA 227 (i.e. 1,1,1,2,3,3,3-heptafluoropropane), or mixtures thereof, and (iv) optionally surfactant, does not reasonably provide enablement for compositions comprising any solvates, any hydrates, or other physiologically acceptable derivatives of ciclesonide and/or formoterol, with the exception of formoterol fumarate dihydrate and the specific 21-hydroxy ciclesonide compounds identified above.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Applicant Claims
2. Determining the scope and contents of the prior art.
3. Ascertaining the differences between the prior art and the claims at issue, and resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3-6, 9, and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aberg et al. (U.S. Patent No. 5,795,564) (IDS) in view of Burt (US 2002/0030068), García-Marcos et al. ("Inhaled corticosteroids plus long-acting beta2-agonists as combined therapy in asthma," *Expert Opin. Pharmacother.*, April 2003, *4(1)*, pp 23-39) ("García"), and Calatayud et al. (U.S. Patent No. 5,482,934) (IDS).

Applicant Claims

Applicants claim a pharmaceutical suspension formulation comprising (i) the active particles of ciclesonide, physiologically functional derivative, solvate, or salt thereof, (ii) particles of formoterol, salt, , physiologically functional derivative, fumarate dihydrate thereof, or solvate thereof, (iii) HFA 134a (i.e. 1,1,1,2-tetrafluoroethane), HFA 227 (i.e. 1,1,1,2,3,3,3-heptafluoropropane), or mixtures thereof, and (iv) optionally surfactant, wherein in some embodiments the surfactant is oleic acid present in an amount ranging from about 0.001-0.1% w/w and other embodiments, wherein the compositions also comprise disodium chromoglycate.

NOTE: The recited intended use of the claimed composition of claim 11 is given little patentable weight, because it does not affect the components of the claimed composition.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Aberg exemplifies a metered dose inhaler containing a suspension formulation comprising (i) **R,R-formoterol fumarate dihydrate**, (ii) trichloromonofluoromethane (propellant), (iii) dichlorodifluoromethane (propellant), and (iv) sorbitan trioleate (surfactant) (Example 12: col. 13, lines 3-20). Aberg teaches that commercially available formoterol is a racemic mixture of the "R,R" and the "S,S" enantiomers and is used **as a bronchodilator in the treatment of respiratory diseases, such as asthma** (col. 1, lines 53-55; col. 2, line 63 through col. 3, line 52; col. 5, lines 11-15, and col. 6, lines 45-50). Aberg teaches that utilizing (R,R)-formoterol is desirable due to its diminished adverse effects, decreased development of tolerance, and increased bronchial distribution upon inhalation administration when compared to racemic formoterol (col. 8, lines 5-10). **Aberg teaches that (R,R)-formoterol may be used in**

and may be formulated into various forms such as **suspensions**, which may be **administered by inhalation** (col. 10, lines 36-60; Example 12: col. 13, lines 3-20; claims 1-3 and 8-12).

Burt teaches that chlorofluorocarbon propellants are being phased out in pharmaceutical formulations, because these propellants deplete the ozone layer [0002] and that **suitable alternative propellants include HFA-134a (1,1,1,2-tetrafluoroethane) and HFA-227 (1,1,1,2,3,3,3-heptafluoropropane)**. Burt identifies several active agents that may be formulated into pharmaceutical compositions in the form of a solution **or a suspension** in combination with HFA propellants, such as **anti-inflammatories (e.g. budesonide, fluticasone, flunisolide, etc.) and bronchodilators (e.g. formoterol)** [0016]. Burt explicitly suggests the combination of a long-acting beta-2 agonist (i.e. salmeterol xinafoate) and an anti-inflammatory steroid (i.e. fluticasone propionate) [0017] in the same pharmaceutical aerosol formulation.

García teaches that data for the **combination of a long-acting beta-2 agonist (e.g. formoterol or salmeterol) with an inhaled corticosteroid (ICS) in the same inhaler is as effective as administration of a much higher dosage of the ICS alone for the control of asthma in patients with asthma that is not well controlled with ICS alone** (abstract; pgs. 23-24, introduction; pg. 34, section 12; and pg. 34-35 1st paragraph of section 13 and last paragraph of section 13) and permits a decreased likelihood of a patient experience side effects from the ICS. Several studies concerning the effectiveness of the combination of formoterol and budesonide in the treatment of asthma are reviewed in section 2.2. García teaches that the **formoterol/budesonide combination was found to improve lung function and asthma control when combined with both low and high doses of budesonide in comparison to**

asthmatics administered only budesonide (pg. 27, left column, paragraph bridging pages 26-27).

Calatayud teaches the syntheses, purification, and isolation of **ciclesonide** and that **ciclesonide is desirable for the treatment of inflammatory conditions**, because it **has a greater therapeutic index** (i.e. a much lower systemic effects and its effects are more localized) **than other commonly administered anti-inflammatory steroids (e.g. budesonide, beclomethasone dipropionate, betamethasone valerate, flunisolide, etc.)** (abstract; col. 1, lines 64-67; Example VII: col. 10, lines 1-44; Table II, compound 7: columns 17-18; Table III, compound 7 under columns 17-18).

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Aberg lacks the teaching of compositions comprising formoterol in combination with ciclesonide. This deficiency is cured by the teachings of (Garcia, Burt, and Calatayud). Aberg lacks the teaching of suspension aerosol formulations comprising HFA-134a and/or HFA 227. This deficiency is cured by the teachings of Burt.

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been prima facie obvious at the time of Applicants' invention to combine the teachings of Aberg and García, Burt, and Calatayud, because Aberg teaches that (R,R)-formoterol, a long-acting beta2-agonist (LABA), may be combined with other therapeutic agents, and the combination of LABAs with inhaled corticosteroids has been demonstrated to be

clinically effective and desirable. An ordinary skilled artisan would have been motivated to combine the teachings of the cited references, because these references all described formulations for the treatment of inflammatory diseases (e.g. asthma). An ordinary skilled artisan would have been motivated to combine (R,R)-formoterol with ciclesonide in lieu of other known inhalable corticosteroids, because ciclesonide has a much greater therapeutic index (i.e. lower systemic effects vis-à-vis its localized therapeutic effects). An ordinary skilled artisan would have been motivated to substitute the chlorofluorocarbon propellants present in Aberg's exemplified suspension aerosol formulation for HFA-134a, HFA 227, or combinations thereof, because CFC's are being phased out in pharmaceutical formulations, due to the damage that CFC's do to the ozone layer, and HFA-134a and HFA 227 are art-recognized as suitable pharmaceutically acceptable propellants for use in lieu of CFC's. Thus, an ordinary skilled artisan would have had a reasonable expectation of successfully formulating suspension formulations of formoterol and ciclesonide with HFA-134a, HFA 227, or combinations thereof.

Regarding the presence of ethanol in amounts less than 3%, none of the prior art references suggest or teach formulations comprising ethanol, thus, meeting this claim limitation. Regarding the number of times a day the claimed formulation is administered, this is an intended use of the claimed composition and does not change the composition claimed. Thus, this limitation is given little patentable weight and is met by the prior art teachings suggesting the composition of claim 1. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

Claims 2 and 7-8 rejected under 35 U.S.C. 103(a) as being unpatentable over Aberg et al. (U.S. Patent No. 5,795,564) (IDS) in view of Burt (US 2002/0030068), García-Marcos et al. ("Inhaled corticosteroids plus long-acting beta2-agonists as combined therapy in asthma," *Expert Opin. Pharmacother.*, April 2003, *4(1)*, pp 23-39) ("García"), and Calatayud et al. (U.S. Patent No. 5,482,934) (IDS) as applied to claims 1, 3-6, 9, and 11 above, and further in view of Fassberg et al. (U.S. Patent No. 5,474,759).

Applicant Claims

Applicants claim a composition as described above, comprising a surfactant and in some embodiments the claimed composition may comprise ethanol.

NOTE: The recited intended use of the claimed composition of claim 11 is given little patentable weight, because it does not affect the components of the claimed composition.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of Aberg, Garcia, Burt, and Calatayud are set forth above.

Fassberg teaches pharmaceutical aerosol formulations comprising (i) **a medicament in an amount from 0.01-1% w/w, (ii) surfactant in an amount of 0-3% w/w; (iii) excipient (e.g. ethanol) in an amount from 0-75% w/w, and (iv) 1,1,1,2,3,3,3-heptafluoropropane (HFC 227) (propellant)**, which was used in lieu of CFC propellants that deplete the ozone layer (title; abstract; col. 1, line 40 through col. 2, line 21). **Preferred surfactants include oleic acid**, sorbitan trioleate, etc. (col. 3, lines 40-55; col. 5, lines 42-46). Surfactants are used to lower the surface and interfacial tension between the medicament and the propellant and may be used in

suspension formulations (col. 5, lines 31-35). The excipient facilitates that compatibility of the medicament with the propellant and also lowers the discharge pressure to an acceptable range (col. 4, lines 55-62). **Preferred excipients include ethanol** (col. 5, lines 4-30). Suitable medicaments are those which are delivered by oral or nasal inhalation and include bronchodilators (e.g. albuterol), anti-inflammatory compounds (e.g. mometasone furoate, disodium chromoglycate, beclomethasone dipropionate, etc.) (col. 6, lines 6-21). Fassberg exemplifies various formulations comprising a beta agonist bronchodilator (i.e. albuterol) (see Example 1-18 in columns7 and 8) as well as formulations comprising anti-inflammatory steroids (see Examples 19-33 in columns 8 and 9).

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Aberg lacks the teaching of formulations comprising ethanol and/or a surfactant. This deficiency is cured by the teachings of Fassberg.

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been prima facie obvious at the time of Applicants' invention to combine the teachings of Aberg and Fassberg, because both references teach inhalable formulations suitable for the treatment of asthma that can be formulated as aerosol formulations with hydrofluorocarbon propellants. An ordinary skilled artisan would have been motivated to modify the teachings of Aberg to include ethanol and or a surfactant, such as oleic acid, because Fassberg teaches that both ethanol and surfactants can be added to tune the formulation surface

tension and facilitate the compatibility of the medicament with the hydrofluorocarbon propellant. An ordinary skilled artisan would have found it prima facie obvious to select ethanol as a possible excipient as well as oleic acid as a possible surfactant, because both ethanol and oleic acid are taught as being a preferred excipient and surfactant, respectively, by Fassberg. Furthermore, it is noted that approximately 1/3 of Fassberg's exemplified compositions contain oleic acid and approximately 1/6 of Fassberg's exemplified compositions contain ethanol. Thus, an ordinary skilled artisan would likely choose both oleic acid and ethanol from the list of preferred excipients and surfactants from which to prepare pharmaceutical aerosol suspension formulations. An ordinary skilled artisan would have had a reasonable expectation of successfully formulating suspension formulations of formoterol and ciclesonide containing ethanol and/or oleic acid, because Fassberg taught that suspension formulations could contain surfactants and/or excipients, such as ethanol.

Regarding the amount of ethanol and oleic acid recited in Applicants' claims, this amount overlaps with the amounts taught as being suitable by Fassberg. A prima facie case of obviousness necessarily exists when the prior art range overlaps or touches a claimed range, such as in the instant rejection. MPEP § 2144.05. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

Claims 1, 3, 5, 9 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gavin et al. (WO 01/78738) ("Gavin") in view of Calatayud et al. (U.S. Patent No. 5,482,934) (IDS).

Applicant Claims

Applicants' claims have been described above.

NOTE: The recited intended use of the claimed composition of claim 11 is given little patentable weight, because it does not affect the components of the claimed composition.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Gavin teaches medicinal compositions comprising (R,R)-formoterol and rofleponide (i.e. a corticosteroid) for the treatment of respiratory diseases, such as asthma, preferably in the form of inhalable compositions (title; abstract; pg. 1, lines 29-33; pg. 2, lines 12-17, and pg. 3, lines 11-21). (R,R)-formoterol may be used in the form of its fumarate salt (pg. 4, lines 17-20). **The invented compositions may comprise additional therapeutic agents, such as anti-inflammatory agents (e.g. budesonide, beclomethasone dipropionate, triamcinolone acetonide, etc.) or NSAIDS (e.g. sodium cromoglycate)** (pg. 6, lines 1-10). Sodium cromoglycate is synonymous with disodium chromoglycate. Inhalable formulations include powders and **suspension aerosols delivered from pressurized packs with the use of a propellant, such as 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane, or mixtures thereof** (pg. 6, line 27 through pg. 7, line 4; Claim 8). The active ingredients in suspension aerosol formulations have a particle size in the range of 1-10 microns, preferably 1-5 microns

(Id.). Gavin exemplifies two metered dose inhaler formulations comprising (R,R)-formoterol fumarate, rofleponide, and 1,1,1,2-tetrafluoroethane (pg. 8, lines 5-25).

The teachings of Calatayud are set forth above.

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Gavin lacks the teaching of formulations comprising ciclesonide. This deficiency is cured by the teachings of Calatayud.

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been prima facie obvious at the time of Applicants' invention to combine the teachings of Gavin and Calatayud, because Calatayud teaches that ciclesonide has a greater therapeutic index than other conventional anti-inflammatory corticosteroids. An ordinary skilled artisan would have been motivated to combine the teachings of the cited references, because it is desirable to utilize a corticosteroid with large therapeutic index, such as ciclesonide, to minimize undesirable systemic effects and maximize the desirable local anti-inflammatory effects. An ordinary skilled artisan would have been motivated to utilize HFA-134a, HFA 227, or combinations thereof, because these propellants are taught by Gavin as being suitable for use in pharmaceutical suspension aerosol formulations. Thus, an ordinary skilled artisan would have had a reasonable expectation of successfully formulating suspension formulations of formoterol and ciclesonide with HFA-134a, HFA 227, or combinations thereof. Regarding the presence of

ethanol in amounts less than 3%, none of the prior art references suggest or teach formulations comprising ethanol, thus, meeting this claim limitation.

Claims 2, 4 and 7-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gavin et al. (WO 01/78738) ("Gavin") in view of Calatayud et al. (U.S. Patent No. 5,482,934) (IDS) as applied to claims 1, 3, 5, 9, and 11 above, and further in view of Fassberg et al. (U.S. Patent No. 5,474,759).

Applicant Claims

Applicants claim a composition as described above, comprising a surfactant and in some embodiments the claimed composition may comprise ethanol.

NOTE: The recited intended use of the claimed composition of claim 11 is given little patentable weight, because it does not affect the components of the claimed composition.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Gavin's teachings are set forth above. The teachings of Calatayud are set forth above.

Fassberg teachings are set forth above.

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Gavin lacks the teaching of formulations comprising ethanol and/or a surfactant. This deficiency is cured by the teachings of Fassberg.

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been prima facie obvious at the time of Applicants' invention to combine the teachings of Gavin and Fassberg, because both references teach inhalable formulations comprising anti-inflammatory steroids that can be formulated as aerosols suspensions with hydrofluorocarbon propellants. An ordinary skilled artisan would have been motivated to modify the teachings of Gavin to include ethanol and or a surfactant, such as oleic acid, because Fassberg teaches that both ethanol and surfactants can be added to tune the formulation surface tension and facilitate the compatibility of the medicament with the hydrofluorocarbon propellant. An ordinary skilled artisan would have found it prima facie obvious to select ethanol as a possible excipient as well as oleic acid as a possible surfactant, because both ethanol and oleic acid are taught as being a preferred excipient and surfactant, respectively, by Fassberg. Furthermore, it is noted that approximately 1/3 of Fassberg's exemplified compositions contain oleic acid and approximately 1/6 of Fassberg's exemplified compositions contain ethanol. Thus, an ordinary skilled artisan would likely choose both oleic acid and ethanol from the list of preferred excipients and surfactants from which to prepare pharmaceutical aerosol suspension formulations. An ordinary skilled artisan would have had a reasonable expectation of successfully formulating suspension formulations of formoterol and ciclesonide containing ethanol and/or oleic acid, because Fassberg taught that suspension formulations could contain surfactants and/or excipients, such as ethanol.

Regarding the amount of ethanol and oleic acid recited in Applicants' claims, this amount overlaps with the amounts taught as being suitable by Fassberg. A prima facie case of obviousness necessarily exists when the prior art range overlaps or touches a claimed range, such

as in the instant rejection. MPEP § 2144.05. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

Claims 2, 4, 7-8, and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gavin et al. (WO 01/78738) ("Gavin") in view of Calatayud et al. (U.S. Patent No. 5,482,934) (IDS) as applied to claims 1, 3, 5, 9, and 11 above, and further in view of Keller et al. (WO 00/07567) (IDS)[1], wherein U.S. Patent No. 6,475,467 (Keller) (IDS) is being used as the English language equivalent of WO 00/07567**.**

Applicant Claims

Applicants claim a composition as described above, further comprising disodium chromoglycate in a non-therapeutically and/or non-prophylactically active concentration, and in some embodiments ethanol and/or a surfactant (e.g. oleic acid).

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Gavin's teachings are set forth above. The teachings of Calatayud are set forth above.

Keller teaches that the inclusion of solid salts of cromoglycic acid and/or nedocromil as a vehicle at non-therapeutically or non-prophylactically effective **concentrations improves the dispersion characteristics and the chemical and physical stability or active ingredients**

which are sensitive to moisture and are present in pharmaceutical aerosol suspension formulations (abstract). **Particularly preferred carrier materials are disodium cromoglycate and nedocromil sodium** (col. 6, lines 32-36). Suitable active agents used in combination with disodium cromoglycate or nedocromil sodium are any that which can be administered as suspended aerosols in therapeutically effective amounts, such as formoterol, formoterol fumarate, and ciclesonide (col. 5, lines 13-29). The aerosol formulations may also **contain a combination of active agents, such as formoterol or a pharmaceutically acceptable derivative, and ciclesonide** (col. 5, lines 36-47).

Keller's compositions do not require the addition of cosolvents or surfactants; however, if a cosolvent and/or surfactant are desired these may be included (col. 4, line 66 through col. 5, line 7 and col. 8, line 59 through col. 9, line 28). Preferred cosolvents, if present, include ethanol (col. 9, lines 4-5). **The amount of cosolvent present is not over about 15% w/w, preferably not over about 10%, usually not over about 5% w/w** (col. 9, lines 8-13). **Suitable surfactants, if present, include oleic acid, and are generally present in an amount ranging from 0.001 to 0.1% w/w** (col. 9, lines 14-28). Keller exemplifies the preparation of an aerosol suspension formulation comprising (i) ~99.93% w/w HFA 227, (ii) ~0.007% w/w of formoterol fumarate, (iii) ~0.014% of disodium cromoglycate, and (iv) ~0.043% of fluticasone propionate in Example 6 (col. 10, lines 50-63).

Keller specifically states that the **inclusion of disodium cromoglycate or nedocromil sodium to formulations can be used to stabilize moisture-sensitive compounds, such as formoterol fumarate** (col. 4, lines 51-59) as well as **to reduce the tendency to adhesion of**

[1] Applicants' March 7, 2006 IDS indicated that U.S. Patent No. 6,475,467 is the English language equivalent of WO

electrostatically charged active compounds, such as micronized corticosteroids (col. 4, lines 60-65).

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Gavin lacks the teaching of formulations comprising (i) disodium cromoglycate in a sub-therapeutic amount and (ii) ethanol and/or a surfactant. This deficiency is cured by the teachings of Keller.

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been prima facie obvious at the time of Applicants' invention to combine the teachings of Gavin and Keller, because both references teach inhalable formulations comprising anti-inflammatory steroids and/or formoterol fumarate that can be formulated as aerosols suspensions with hydrofluorocarbon propellants (e.g. HFA 227). An ordinary skilled artisan would have been motivated to modify the teachings of Gavin to include disodium cromoglycate to obtain suspension formulations exhibiting improved physical and chemical stability (Keller). Furthermore, an ordinary skilled artisan would have been motivated to include ethanol and or a surfactant, such as oleic acid, because Keller teaches that both ethanol and surfactants can be added to the suspension formulation and specifies suitable amounts of cosolvent and surfactants that can be added if desired. An ordinary skilled artisan would have had a reasonable expectation of combining the teachings of Gavin and Keller, because both

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WO 00/07567 (i.e. "corresponds to…").

references teach HFA-based pharmaceutical suspensions and Keller teaches amounts of disodium cromoglycate as well as amounts of ethanol and oleic acid, if present, that can be suitably co-formulated with compositions comprising medicaments, such as formoterol fumarate and a corticosteroid.

Regarding the amount of ethanol recited in Applicants' claims, this amount overlaps with the amounts taught as being suitable by Keller. A prima facie case of obviousness necessarily exists when the prior art range overlaps or touches a claimed range, such as in the instant rejection. MPEP § 2144.05. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1 and 5 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 6 of copending Application No. 10/537,356 (copending '356) in view of Burt (US 2002/0030068) and Aberg et al. (U.S. Patent No. 5,795,564) (IDS).

Claim 1 of the instant application has been described above. Independent claim 6 of copending '356 claims a formulation comprising R,R-formoterol and ciclesonide in a form administrable from a dry powder inhaler. The difference between claim 1 of the instant application and claim 6 of copending '356 is that the composition of the instant application is a suspension formulation (i.e. it comprises insoluble particulate formoterol and particulate ciclesonide) and claim 1 of the instant application does not specify that formoterol is (R,R)-formoterol. Regarding (R,R)-formoterol, the use of this enantiomer is prima facie obvious at the time of the instantly claimed invention, because it was known to be the broncho-active enantiomer of the commercially available racemic formoterol mixture (Aberg). Regarding conversion of a mixture of particulate formoterol and ciclesonide into a suspension, this requires the mere addition of HFA propellant, which can be done by various well known procedures (e.g. cold filling of the propellant into a metered dose inhaler pre-filled with a particulate mixture). Furthermore, inhalable aerosol suspensions are one of the conventionally used inhalable formulations (i.e. (i) inhalable aerosol solutions, (ii) inhalable aerosol suspensions, (iii) propellant-free solutions, (iv) propellant-free suspensions, and (v) inhalable powders). Aerosol suspensions comprising a mixture of a beta2-agonist with an anti-inflammatory steroid are well known (Burt). Therefore, a person of ordinary skill in the art at the time of the instant invention would have found claims 1 and 5 *prima facie* obvious over claim 6 of copending Application No.

10/537,356 (copending '356) in view of Burt (US 2002/0030068) and Aberg et al. (U.S. Patent No. 5,795,564) (IDS).

This is a provisional obviousness-type double patenting rejection.

Conclusion

Claims 1-11 are rejected. Claims 2, 4, 8, and 10 are objected. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James H. Alstrum-Acevedo whose telephone number is (571) 272-5548. The examiner can normally be reached on M-F, ~10:00-6:00 and Saturdays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on (571) 272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/James H Alstrum-Acevedo/
Patent Examiner, Art Unit 1616
Technology Center 1600